THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Gayet-Ageron A, Prieto-Merino D, Ker K, et al, for the Antifibrinolytic Trials Collaboration. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. *Lancet* 2017; published online Nov 7. http://dx.doi.org/10.1016/S0140-6736(17)32455-8.

Web extra materials

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Web extra material 1. MEDLINE search strategy.

The searches used to identify trials for this study were run to 7 April 2017 and were not restricted by date, language or publication status.

Database: Ovid MEDLINE(R) <1946 to March Week 5 2017>

1 exp Antifibrinolytic Agents/

2 (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or ((plasmin or fibrinolysis) adj3 inhibitor*)).ab,ti.

3 exp Aprotinin/

4 (Aprotinin* or kallikrein-trypsin inactivator* or bovine kunitz pancreatic trypsin inhibitor* or bovine pancreatic trypsin inhibitor* or basic pancreatic trypsin inhibitor* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin* or Trasylol or Antilysin Spofa or rp?9921 or antagosan or antilysin or antilysine or apronitin* or apronitrine or bayer a?128 or bovine pancreatic secretory trypsin inhibitor* or contrycal or frey inhibitor* or gordox or kallikrein trypsin inhibitor* or kazal type trypsin inhibitor* or (Kunitz adj3 inhibitor*) or midran or (pancrea* adj2 antitrypsin) or (pancrea* adj2 trypsin inhibitor*) or riker?52g or rp?9921or tracylol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren).ab,ti.

5 exp Tranexamic Acid/

6 (tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA).ab,ti.

7 exp Aminocaproic Acids/ or exp 6-Aminocaproic Acid/

8 (((aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic) adj2 acid*) or epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or lederle or Aminocaproic or aminohexanoic or amino caproic or amino n hexanoic or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl 10304 or EACA or eaca roche or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or tachostyptan).ab,ti.

9 exp 4-Aminobenzoic Acid/tu [Therapeutic Use]

10 (PAMBA or para-aminomethylbenzoic or p-aminomethylbenzoic or amino?methylbenzoic acid or Gumbix or Styptopur or H-4-AMB-OH or CAS:56-91-7 or H-4AMBZ-OH or NH2-CH2-PH4-COOH or TIMTEC-BB SBB006704 or "RARECHEM AL BW 0005" or Amino-p-toluicacid).ti,ab.

11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 10

12 randomi?ed.ab,ti.

13 randomized controlled trial.pt.

14 controlled clinical trial.pt.

15 placebo.ab.

16 clinical trials as topic.sh.

17 randomly.ab.

18 trial.ti.

19 12 or 13 or 14 or 15 or 16 or 17 or 18

20 (animals not (humans and animals)).sh.

21 19 not 20

22 11 and 21

Web extra material 2. Equations of the different models.

1) Logistic regression assessing overall treatment effect and homogeneity of treatment effect across trials

$$\text{Logit}\,(p(Y = 1)) = \beta_0 + \beta_1\, S + \beta_2\, X + \beta_3\, (X*S) \qquad \text{[model-1]}$$

With Y = 1, the outcome did not die from bleeding for patient i in trial j, S is the trial (CRASH-2 S=0, WOMAN S=1), X is treatment (tranexamic acid is X=1, placebo is X=0).

Then β_0 is the log(odds) in the placebo group in the CRASH-2 trial, β_1 is the difference between trials in placebo group, β_2 the effect of tranexamic acid in CRASH-2 trial, and β_3 is the interaction between treatment effect and trial.

2) Logistic regression estimating non-linear effect of intervention by treatment delay and its interaction with trial (triple interaction).

$$\text{Logit}\,(p(Y = 1)) = \beta_0 + \beta_1\, S + \beta_2\, X + \beta_3\, (X*S) + \beta_4\, T + \beta_5\, T^2 + \beta_6\, (T*S) + \beta_7\, (T^2*S) \text{ ++ } \beta_8\, A + \beta_9\, SBP + \beta_{10}\, (T*X) + \beta_{11}\, (T^2*X) + \beta_{12}\, (T*S*X) + \beta_{13}\, (T^2*S*X)$$

[model-2]

With Y, S, X coded as in [model-1]. T is treatment delay in hours (and T^2 being hours squared), A is age by 10-year intervals, SBP is systolic blood pressure by 5-mmHg intervals.

Then β_0 is the log(odds) in the placebo group in the CRASH-2 trial when T=0; β_1 is the difference between trials in placebo group at T=0; β_2 the effect of tranexamic acid in CRASH-2 trial at T=0; β_3 is the interaction between treatment effect and trial at T=0; β_4 and β_5 are the linear and quadratic effects respectively of treatment delay in the placebo group of the CRASH-2 trial; β_6 and β_7 are the differences between trials of the effects of treatment delay in the placebo group; β_8 is the effect of age and β_9 is the effect of SBP; β_{10} and β_{11} are the interactions of treatment delay and treatment delay squared, respectively, with the treatment in the CRASH-2 trial; β_{12} and β_{13} are the triple interactions of treatment delay with the treatment and treatment delay squared, respectively, with trial.

3) Logistic regression estimating non-linear effect of intervention by treatment delay (we assume this interaction is the same in both trials).

$$\text{Logit}\,(p(Y = 1)) = \beta_0 + \beta_1\, S + \beta_2\, X + \beta_4\, T + \beta_5\, T^2 + \beta_6\, (T*X) + \beta_7\, (T^2*X) + \beta_8\, A + \beta_9\, SBP \qquad \text{[model-3]}$$

With Y, S, X, T, A, SBP coded as in [model-1] and [model-2];

Then, β_0 is the log(odds) in the placebo group in the CRASH-2 trial when T=0; β_1 is the difference between trials; β_2 the effect of tranexamic when T=0; β_4 and β_5 are the linear and quadratic effects of treatment delay in the placebo group of both trials; β_6 and β_7 are the interactions of treatment delay with the treatment and treatment squared, respectively; β_8 is the effect of age and β_9 is the effect of SBP.

Web extra material 3. Characteristics of included and ongoing trials.

Trial ID	Title	Participants	Intervention	Outcomes
Included trials				
CRASH-2[1]	A large randomised placebo controlled trial among trauma patients with, or at risk of, significant haemorrhage, of the effects of anti-fibrinolytic treatment on death and transfusion requirement.	N=20,211 Adult (>16 years) trauma patients with, or at risk of, significant bleeding.	A loading dose of 1 g tranexamic acid or placebo will be administered as soon possible, followed by a maintenance dose of 1 g TXA or placebo over eight hours.	Primary: Death. Secondary: Vascular occlusive events, blood transfusion requirements, disability.
WOMAN[2]	Tranexamic acid for the treatment of postpartum haemorrhage: an international randomised, double blind, placebo controlled trial	N=20,060 Women with clinically diagnosed postpartum haemorrhage following vaginal delivery of a baby or caesarean section. The clinical diagnosis of PPH may be based on any of the following: estimated blood loss after vaginal delivery of a baby> 500 mL OR >1000 mL from caesarean section OR blood loss sufficient to compromise the haemodynamic status of the woman.	1g of T tranexamic acid by intravenous injection or placebo (sodium chloride 0.9%) given as soon as possible after randomisation. If after 30 minutes bleeding continues, or if it stops and restarts within 24 hours after the first dose, a second dose may be given.	Primary: Death or hysterectomy. Secondary: Death, surgical intervention, blood transfusion, health status, thromboembolic events, other relevant medical events, length of stay at hospital/time spent at an intensive care unit, mechanical ventilation, status of breastfed baby/ies.
ATACAS[3]	Aspirin and tranexamic acid for Coronary Artery Surgery Trial	N=4662 Adults undergoing coronary-artery surgery and at risk of perioperative complications.	Tranexamic acid (100mg/kg) or saline administered 30 minutes after induction of anaesthesia (dose of tranexamic acid halved to 50mg after 1392 patients enrolled)	Primary: Composite outcome of all-cause 30 day mortality or thrombotic event Secondary: Death, nonfatal myocardial infarction, pulmonary embolism, stroke, acute renal failure, bowel infarction), reoperation due to major haemorrhage or cardiac tamponade, blood transfusion.
Ongoing trials				
Beverland (EUCTR2015-002661-36-GB) Expected completion date: December 2018	Single centre randomised controlled trial to assess the effect of the addition of twenty-four hours of oral tranexamic acid post-operatively to a single intra-operative intravenous dose of tranexamic acid on calculated blood loss following primary hip and knee arthroplasty.	N=1166 (target) Adults undergoing primary elective hip or knee replacement.	Intervention group 1: 1g IV tranexamic acid during operation plus 1g oral tranexamic acid at 2, 10, 18 and 26 hours after operation. Intervention group 2: 1g IV tranexamic acid during operation. Control: standard care (no tranexamic acid)	Primary: indirectly calculated blood loss 48 hrs post-surgery calculated using red cell counts before and after surgery. Secondary: Incidence of postoperative haemoglobin levels falling below transfusion trigger, c-reactive protein level, creatinine level, 90 day mortality, one year mortality.
CRASH-3 (ISRCTN15088122)[4] Expected completion date: December 2018	Tranexamic acid for the treatment of significant traumatic brain injury: an international randomised, double blind placebo controlled trial	N=13,000 (target) Adults with traumatic brain injury, who are within eight hours of injury, with any intracranial bleeding on CT scan or who have a GCS of 12 or less, and have no significant extra-cranial haemorrhage.	Loading dose of tranexamic acid (1 gram by intravenous injection) or placebo (sodium chloride 0.9%) given as soon as possible after randomisation. Maintenance dose of tranexamic acid (1 gram by intravenous injection) or placebo (sodium chloride 0.9%) given after the loading dose is finished.	Primary: death in hospital within 28 days of injury. Secondary: vascular occlusive events, disability, seizures, neurosurgical intervention, days in intensive care, other adverse events.
HALT-IT	Tranexamic acid for the treatment of	N=8000 (target)	Loading dose of tranexamic acid (1g by	Primary: death in hospital (cause-specific

(ISRCTN11225767)[5] Expected completion date: October 2017	gastrointestinal haemorrhage: an international randomised, double blind placebo controlled trial	Adults with acute significant upper or lower gastrointestinal bleeding.	intravenous injection) or placebo (sodium chloride 0.9%) will be given as soon as possible after randomisation, followed by an intravenous infusion of 3g of tranexamic acid or placebo (sodium chloride 0.9%) over 24 hours.	mortality will also be recorded) Secondary: Re-bleeding, need for salvage surgery or radiological intervention, blood transfusion, thromboembolic events, other adverse medical events, functional status, time spent at an intensive care unit, length of stay in hospital
Li (NCT01060176) Expected completion date: March 2016	A Multicenter Clinical Trial of Tranexamic acid on Blood Loss and Allogeneic Transfusions in Cardiopulmonary Bypass Cardiac Surgery	N=1200 (target) Rheumatic or recessive valvular disease patients requiring valvular replacement surgery with cardiopulmonary bypass Coronary artery disease patients requiring coronary artery bypass surgery with cardiopulmonary bypass	Intervention 1: A loading dose of 30 mg/kg and a maintenance infusion of 20 mg/kg/h Intervention 2: A loading dose of 20 mg/kg and a maintenance infusion of 15 mg/kg/h Intervention 3: A loading dose of 10 mg/kg and a maintenance infusion of 10 mg/kg/h Control: Routine therapy without tranexamic acid	Primary: Blood loss (chest drainage) postoperatively; allogeneic transfusions Secondary: Length of stay in ICU and hospital postoperatively; Rate of reexploration for hemostasis; coagulatory and fibrinolytic status; inflammatory cytokines; thromboelastography
NCT02936661 Expected completion date: March 2019	Tranexamic acid for Preventing Postpartum Hemorrhage After Cesarean Section	N=6700 (target) Women giving birth by cesarean section.	Tranexamic acid or placebo	Primary: postpartum haemorrhage Secondary: the amount of postpartum bleeding
PATCH (NCT02187120)[6] Expected completion date: December 2017	A Multi-centre Randomised, Double-blinded, Placebo-controlled Trial of Pre-hospital Treatment With tranexamic acid for Severely Injured Patients at Risk of Acute Traumatic Coagulopathy.	N= 1184 (target) Adult patients (age ≥18 years); injured through any mechanism; COAST score≥3.	1g tranexamic acid or placebo (0.9% NaCl) by slow intravenous injection as early as possible following injury. Soon after arrival to the emergency department, patients will be given 1g tranexamic acid or placebo infused intravenously for 8 hours.	Primary: Favourable outcome at six months (moderate disability to good recovery, GOSE scores 5-8) compared to those who have died (GOSE 1), or have severe disability (GOSE 2-4). Secondary: Units of blood products used in the first 24 hours; coagulation profile; ICU ventilator-free days in first 28 days; vascular occlusive events; mortality; proportion of deaths due to: bleeding, vascular occlusion, multi-organ failure and head injury; cumulative incidence of sepsis at 28 days or hospital discharge whichever occurs first; severity of chronic pain 6 months after injury and its interference with daily activities measured using the modified Brief Pain Inventory; Quality of life (SF12® and EQ5D) at 6 months.
TICH-2 (EUCTR2012-004108-37-GB)[7] Expected completion date: December 2017	Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage	N=2000 (target) Adult patients with acute primary intracerebral haemorrhage within 8 hours of stroke onset.	Tranexamic acid 1 g or placebo in 100 ml sodium chloride 0.9% infusion bag intravenously as a loading dose infusion over 10 min, followed by infusion of tranexamic acid 1 g or placebo in 250 ml sodium	Primary: Death or dependency at day 90 Secondary: Neurological impairment at day 7 or discharge if sooner, disability (Barthel index) at day 90, Quality of Life (EuroQol) at day 90, cognition at day 90, costs: length of stay in hospital, re-

			chloride 0.9% infusion bag over 8 h.	admission, institutionalisation, radiological efficacy/safety (CT scan): change in haematoma volume from baseline to day 2, haematoma location and new infarction.
STAAMP (NCT02086500)[8] Expected completion date: March 2018	Study of tranexamic acid During Air Medical Prehospital Transport Trial For Trauma Patients At Risk Of Hemorrhage	N=1000 (target) Adult (18-90 years) trauma patients within 2 hours of injury. Setting: USA	1g tranexamic acid or placebo during air medical transport.	Primary outcome: 30 day mortality. Secondary outcomes: hyperfibrinolysis, acute lung injury, multiple organ failure, nosocomial infection, mortality, early seizures, pulmonary embolism, early resuscitation needs, early coagulopathy as measured by INR and rapid thromboelastography parameters, early inflammatory response, plasmin levels, leukocyte, platelet and complement activation.
TRAAP (NCT02302456)[9] Expected completion date: May 2017	Tranexamic acid for Preventing Postpartum Haemorrhage Following a Vaginal Delivery: a Multicenter Randomised Double Blind Placebo Controlled Trial	N = 4000 (target) Women in labour for a planned vaginal singleton delivery, at a term ≥ 35 weeks.	1g tranexamic acid or placebo will be administered intravenously just after birth.	Primary: incidence of PPH, defined by blood loss ≥500 mL Secondary: Mean blood loss at 15 minutes after birth; mean total blood loss; incidence of severe PPH; need for supplementary uterotonic treatment; postpartum transfusion; need for invasive second-line procedures for PPH; haemoglobin, hematocrit; hemodynamic tolerance; mild adverse effects; tolerance lab tests; severe adverse effects

References

1. CRASH-2 Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010; **376**:23-32.
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3. Myles PS, Smith JA, Forbes A, et al. Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery. *N Engl J Med* 2017;**376**:136-48.
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7. Sprigg N, Robson K, Bath P, Dineen R, Roberts I, Robinson T, Roffe C, Werring D, et al. Intravenous tranexamic acid for hyperacute primary intracerebral hemorrhage: Protocol for a randomized, placebo-controlled trial. *Int J Stroke* 2016;**11**:683-94.

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Web extra material 4. Results of risk of bias assessment.

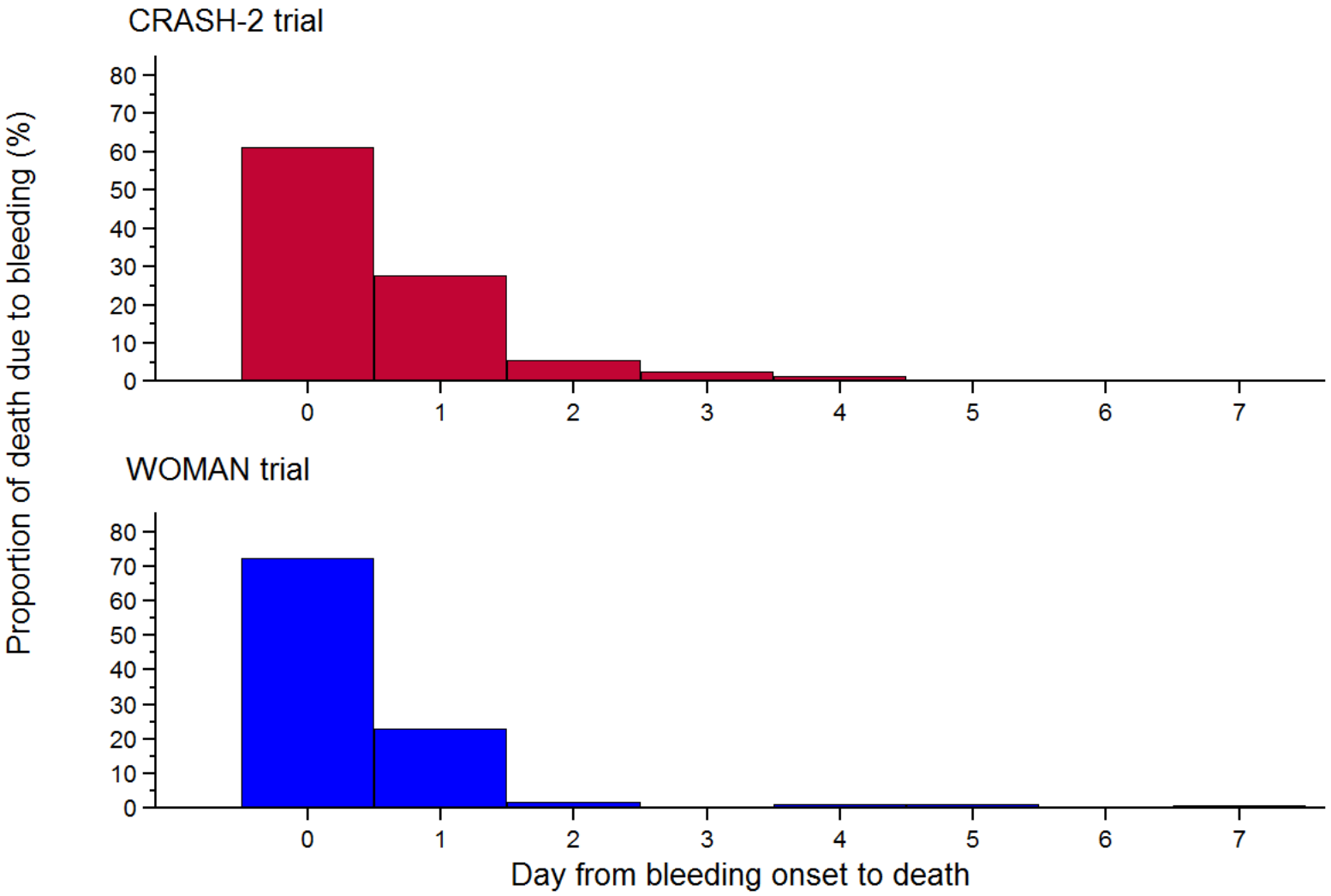
CRASH-2

Domain	Judgement	Justification
Sequence generation	Low	Computer-generated.
Allocation concealment	Low	Tranexamic acid and placebo were packaged in identical ampoules. Recruiting hospitals with reliable telephone access used a telephone randomisation service, hospitals without, used a local pack system.
Blinding	Low	Participants, clinicians and trial staff were blinded to treatment allocation.
Incomplete outcome data	Low	Over 99% of patients were followed up and contributed outcome data.
Selective outcome reporting	Low	Prospectively registered and data on all pre-specified outcomes available for analysis.

WOMAN

Domain	Judgement	Justification
Sequence generation	Low	Computer-generated.
Allocation concealment	Low	Tranexamic acid and placebo were packed in sequentially numbered, sealed, treatment boxes.
Blinding	Low	Participants, clinicians and trial staff were blinded to treatment allocation.
Incomplete outcome data	Low	Over 99% of patients were followed up and contributed outcome data.
Selective outcome reporting	Low	Prospectively registered and data on all pre-specified outcomes available for analysis.

Web extra material 5. Day from randomisation to death due to bleeding in the two trials.

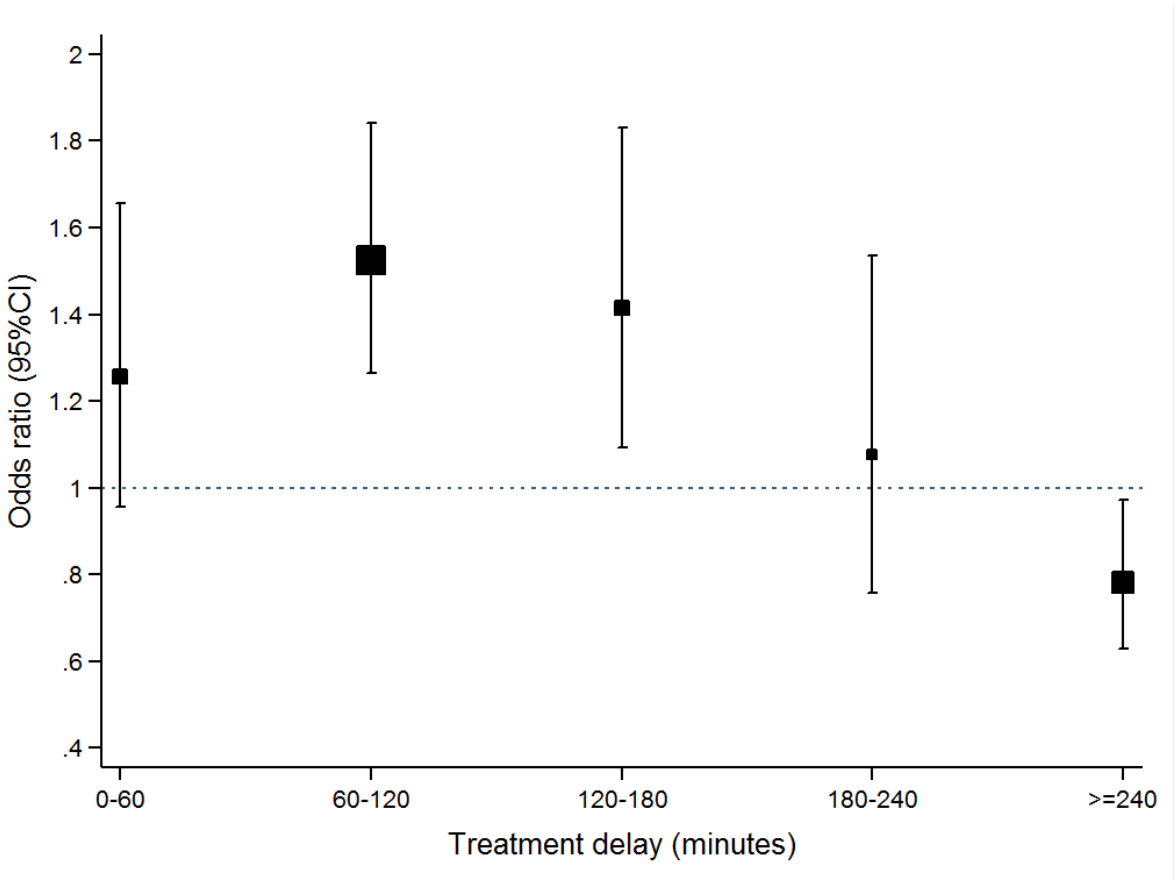


Web extra material 6. Effect of tranexamic acid on primary outcome and vascular occlusive events (fatal and non-fatal) by trial and overall.

	Tranexamic acid n (%)	**Placebo** n (%)	**Odds ratio** (95% CI)
No death due to bleeding			
CRASH-2	8597 (94·6%)	8454 (93·6%)	1·19 (1·05-1·35)*
WOMAN	9807 (98·4%)	9722 (98·1%)	1·24 (0·99-1·53)*
Overall	18,404 (96·6%)	18,176 (96·0%)	1·20 (1·08-1·34)*
p-value for interaction=0·7243			
Death due to vascular occlusive event			
CRASH-2	33 (0·3%)	48 (0·5%)	0·69 (0·44-1·08)
WOMAN	10 (0·1%)	11 (0·1%)	0·90 (0·38-2·12)
Overall	43 (0·2%)	59 (0·3%)	0·73 (0·49-1·09)
p-value for interaction=0·5956			
Myocardial infarction			
CRASH-2	35 (0·3%)	55 (0·5%)	0·64 (0·42-0·98)
WOMAN	2 (0·0%)	3 (0·0%)	0·66 (0·11-3·95)
Overall	37 (0·2%)	58 (0·3%)	0·64 (0·43-0·97)
p-value for interaction=0·9788			
Stroke			
CRASH-2	57 (0·6%)	66 (0·7%)	0·87 (0·61-1·24)
WOMAN	8 (0·1%)	6 (0·1%)	1·32 (0·46-3·81)
Overall	65 (0·3%)	72 (0·4%)	0·91 (0·65-1·27)
p-value for interaction=0·4647			
Pulmonary embolism			
CRASH-2	72 (0·7%)	71 (0·7%)	1·02 (0·74-1·42)
WOMAN	17 (0·2%)	20 (0·2%)	0·84 (0·44-1·61)
Overall	89 (0·4%)	91 (0·5%)	0·98 (0·73-1·32)
p-value for interaction=0·6025			
Deep vein thrombosis			
CRASH-2	40 (0·4%)	41 (0·4%)	0·98 (0·63-1·52)
WOMAN	3 (0·0%)	7 (0·1%)	0·42 (0·11-1·64)
Overall	43 (0·2%)	48 (0·2%)	0·90 (0·60-1·36)
p-value for interaction=0·2483			

* Odds ratios for survival from bleeding.

Web extra material 7. Relative treatment benefit observed by 60-minute interval of treatment delay.



Sizes of boxes for the odds ratios were proportional to the weight of time interval.

Web extra material 8. Number of deaths due to bleeding per treatment allocation, proportional treatment benefit and 95% confidence interval by 60-minute treatment delay.

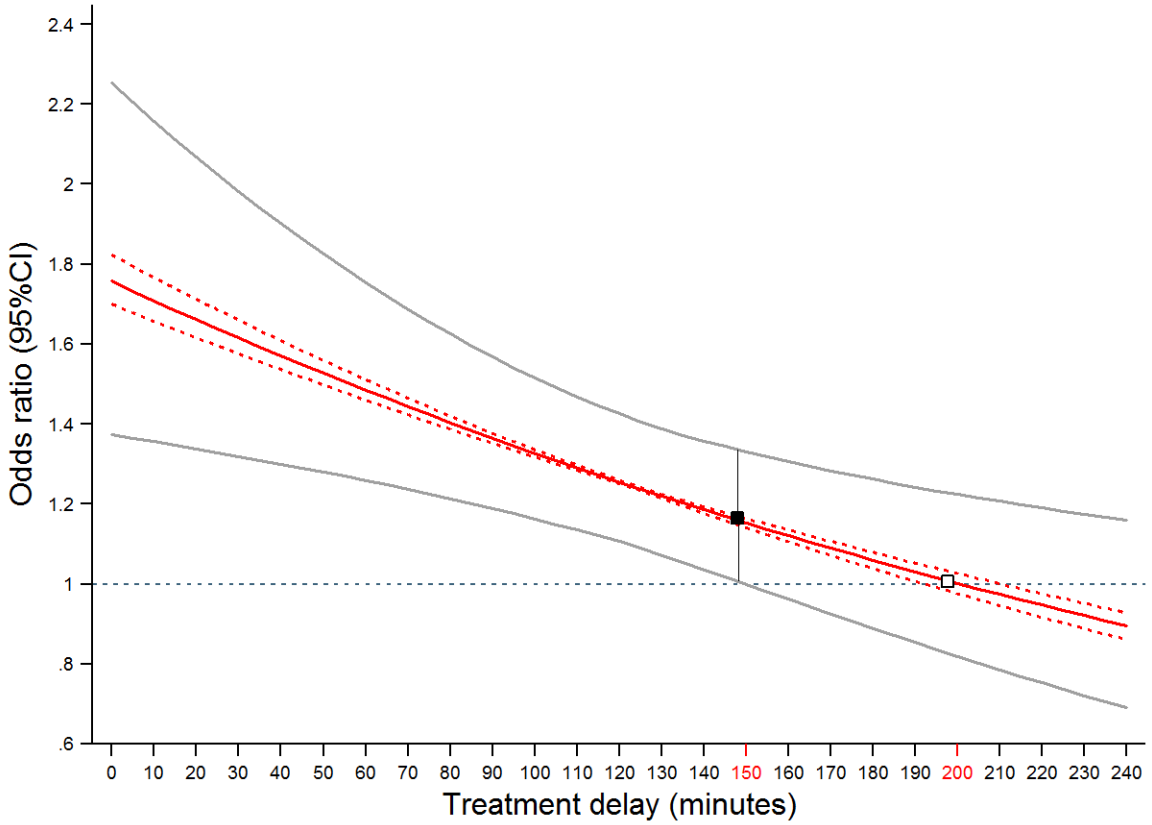
	Tranexamic acid (n=20,040*)	**Placebo** (n=19,981**)	**Odds ratio** (95%CI)
Treatment delay (minutes)			
0-60	94 (1·7%)	115 (2·2%)	1·26 (0·96-1·66)
60-120	192 (3·9%)	283 (5·8%)	1·53 (1·27-1·84)
120-180	104 (3·8%)	146 (5·3%)	1·42 (1·09-1·83)
180-240	61 (3·2%)	66 (3·5%)	1·08 (0·76-1·54)
240-300	64 (4·3%)	47 (2·9%)	0·67 (0·45-0·98)
300-360	43 (4·4%)	35 (3·6%)	0·80 (0·51-1·27)
360-420	37 (4·0%)	30 (3·2%)	0·78 (0·48-1·28)
420-480	20 (3·0%)	14 (2·1%)	0·70 (0·35-1·39)

* 4 missing time to treatment in CRASH-2 trial and 50 observations with time to treatment above 24 hours deleted from WOMAN trial.
** 4 missing time to treatment in CRASH-2 trial and 59 observations with time to treatment above 24 hours deleted from WOMAN trial.

Web extra material 9. Characteristics of patients who died from exsanguination by treatment delay (within first hour versus after one hour).

	Treatment delay 0-60 minutes (n=209)	Treatment delay after 60 minutes (n=1,198)	P-value
Trial, n (%)			<0·0001
CRASH-2	117 (56·0)	945 (78·9)	
WOMAN	92 (44·0)	253 (21·1)	
Female gender, n (%)	107 (51·2)	417 (34·8)	<0·0001
Mean age (years) (±SD, median, IQR)	33·0 (±11·8, 31, 26-37)	35·2 (±14·5, 32, 25-41)	0·0325
Mean systolic blood pressure (mmHg) (±SD, median, IQR)	69·0 (±32·4, 73, 60-90)	71·6 (±32·2, 77, 60-90)	0·2857
Mean heart rate per minute (±SD, median, IQR) (CRASH-2)	107·0 (±34·2, 114, 100-127)	111·0 (±25·8, 115, 100-128)	0·1517
Type of injury, n (%) (CRASH-2)			<0·0001
Blunt	31 (26·5)	453 (47·9)	
Penetrating	67 (57·3)	340 (36·0)	
Both	19 (16·2)	152 (16·1)	
Mean volume of blood loss (mL) (±SD, median, IQR) (WOMAN)	2136·0 (±890·6, 2000, 1500-2550)	2249·0 (±893·9, 2000, 1500-3000)	0·2988

Web extra material 10. Overall effect of treatment delay on treatment benefit after correction for time since injury in CRASH-2 and time since delivery in WOMAN.



The solid red line shows the average model for the odds ratio of not dying from bleeding (proportional treatment benefit) estimated from 100 simulations. The red dashed lines are the lowest and highest estimates obtained from 100 simulations. The grey solid lines are the average upper and lower bounds of the 95% confidence interval obtained from 100 simulations. The white square shows the time point at which the models estimate a null effect of tranexamic acid (a treatment delay of 200 min). The black square shows the time point at which the lower 95%CI models estimate a null effect of tranexamic acid (a treatment delay of 150 min).